Do trained reproductive endocrinologists perform better than their trainees? Comparing clinical pregnancy rates and live birth rates after transfer of single fresh blastocysts

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Received: 4 October 2017 / Accepted: 23 January 2018 / Published online: 9 February 2018
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Abstract

Purpose To compare clinical pregnancy rates and live birth rates of single blastocyst transfers performed by attending physicians or fellows in reproductive endocrinology and infertility program.

Methods Retrospective study in an academic reproductive center. We evaluated 932 fresh single blastocyst transfer cycles performed by fellows in training (389 embryo transfers) and by attending physicians (543 embryo transfers).

Results There were no differences in the baseline characteristics and IVF cycle parameters between patients who had transfers performed by fellows or attending physicians. Transfers performed by attending physicians or fellows resulted in similar CPR (46.5 vs. 42.9%, $p = 0.28$) and LBR (38.3 vs. 34.2%, $p = 0.11$). Multivariate logistic regression analysis showed that even after adjusting for possible confounders (age, gravity, parity, baseline FSH, antral follicle count, dose of gonadotropins, stimulation protocol, and quality of embryo transferred), CPR (OR 0.81, CI 0.62–1.07) and LBR (OR 0.79, CI 0.6–1.05) in the two groups were comparable.

Conclusion Clinical pregnancy rate and live birth rate after embryo transfer performed by attending staffs or fellows are comparable. This finding reassures fellowship programs that allowing fellows to perform embryo transfers does not compromise the outcome.

Keywords Single blastocyst transfer · Fellows in training · Embryo transfer

Introduction

As women are delaying childbearing, the prevalence of infertility rises leading to increasing demand for in vitro fertilization (IVF) [1]. Most countries with high fertility rates also have a higher number of assisted reproductive cycles suggesting that IVF has become an integral part of population growth [1]. As a result, there has been an increasing need to train more gynecologists to become reproductive endocrinologists, and the demand for well-structured fellowship training programs is increasing [2].

An integral part of IVF is oocyte retrievals and embryo transfers [3–6]. The outcome of IVF depends on several factors including the quality and number of embryo transferred, the degree of difficulty of the embryo transfer (ET), and the patient's age and gravity [5–7]. Other important factors are the technique of loading the embryo into the catheter by the embryologist, the speed of injection of the embryo into the uterus, and the intrauterine location where the embryo is deposited [5, 8, 9]. The experience of the operator in performing embryo transfer also affects the overall success of IVF-ET.

In a survey of reproductive endocrinology and infertility fellowship programs, 44% of respondents reported lack of training in ETs during their fellowship [10]. Indeed, there is a variety of teaching protocols among different fellowship programs. Some programs do not allow fellows to perform ET [10–12] and using intrauterine insemination (IUI) or mock ET transfers as a teaching technique [13]. Others proposed artificial models that can be used for learning purposes [14]. IUIs and mock ETs may be similar to an ET, yet they are not

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exactly the same as performing an actual transfer with an embryo. In addition, the learning curve of trainees varies [8, 12]. One of the reasons of not allowing fellows to perform ET is the fear of reducing the pregnancy rates.

The technique of performing an embryo transfer differs between clinics, with most centers doing it under ultrasound guidance [4, 15]. Other factors including the type of catheter used, the position of the catheter during the transfer, and the type of media used also play a role in affecting the pregnancy rates [5, 15–17]. Therefore, when evaluating the role of the operator on pregnancy rates after ETs, it may not be possible to combine data from different clinics.

In our center, fellows' training includes a combination of clinical and operative duties. Fellow duties include seeing patients in clinic to plan IVF cycles, performing ultrasounds for IVF cycle monitoring, and performing operative procedures such as egg collections and embryo transfers. For embryo transfer, fellows are expected to observe all the different trained staff perform embryo transfers, then mock transfers performed by the fellow are observed by the trained staff and scored on a written procedure sheet. Once the fellows are judged to have reached competence by the trained staff, then the fellows are observed performing real embryo transfer and these are similarly scored on a written procedure sheet. Once they have been judged competent by the trained staff, then the fellows perform embryo transfer solo. All embryo transfers are performed under ultrasound guidance. The purpose of our study was to compare clinical pregnancy rates and live birth rates of single blastocyst transfers performed by attending physicians or fellows in reproductive endocrinology and infertility program.

Materials and methods

We evaluated 932 fresh single blastocyst transfer cycles performed by fellows (389 embryo transfers) and by attending physicians (543 embryo transfers) between January 2012 and June 2015. All IVF cycles during this period were funded by the government of Quebec. The Research and Ethics Board of the McGill University Health Centre approved the study (Study 15-249). Cycles with donor oocytes and pre genetic screening or diagnosis were excluded. Fellows were then subcategorized into two groups, junior fellows (first year of training) and senior fellows (second year of training).

Patients underwent stimulation with different IVF protocols including fixed antagonist protocol, mid luteal long agonist protocol, or microdose flare protocol. This was based on the preference of the treating physician. Cycles were monitored with ultrasounds and estradiol levels, until three or more lead follicles reached a size of ≥ 17 mm. HCG or recombinant

HCG was then administered. Ultrasound-guided oocyte retrieval was performed 35–38 h after. Luteal phase was supported with oral estradiol and vaginal progesterone until the pregnancy test was performed. If the test was positive, patients continued luteal support until 12 weeks of pregnancy; otherwise, luteal support was discontinued.

Embryos were cultured in COOK medium (Medical, Sydney, Australia) during all stages of embryo development. Extended culture to blastocyst was performed using the sequential media system. Embryos are scored by the Gardner criteria based on the size of the blastocyst and the assessment of the inner cell mass (ICM) and trophectoderm development. Good quality embryos (Gardner score $\geq 3BB$, grade 1–2) were defined as those where at least the blastocoele completely fills the embryo, the ICM is loosely grouped with several cells, and the trophectoderm has very few cells forming a loose epithelium [18]. Embryos with Gardner score of $< 3BB$ on day 5 were defined as poor quality embryos (grade 3 or 4) [19]. The clinic policy is to avoid transferring grade 4 embryos, except in cases where only these embryos are available.

Embryo transfer was performed 5 days after oocyte retrieval when the embryo reached a blastocyst stage. All transfers were done under abdominal ultrasound guidance. All fellows had to observe at least 10 transfers before they were allowed to do one. Fellows were scheduled to do the transfers once a week and did an average of three transfers per day. All ETs were performed with a Wallace catheter using an afterload technique. The cervix was gently washed with sterile water, and the catheter was introduced into the cervical canal under ultrasound guidance just past the internal cervical os. The inner sheath was then removed, and the embryo loaded into a new catheter by the embryologist. The inner catheter with the embryo was threaded into the outer catheter and the embryo was transferred 1–2 cm below the fundus.

Serum β HCG level was measured 11 days after the transfer, and a viability scan scheduled 2 weeks after a positive β HCG. Clinical pregnancy was defined as an intrauterine pregnancy with visible fetal cardiac activity at gestational age of 6–7 weeks. Livebirth was defined as a live born after 24 weeks of gestation and a birthweight of > 500 g.

Statistical analysis

As the data were normally distributed, demographic characteristics, ovarian stimulation variables, and main pregnancy-related outcome variables of the two study groups were compared using the Student's *t* test for continuous variables. Chi-squared test was used for proportions. All tests were conducted at two-sided 0.05 level of significance. We used SAS version 9.4 software (SAS Institute, Cary, NC) for all statistical analyses. The difference in pregnancy outcome variables

(clinical pregnancy and live birth) between the study groups was assessed by logistic regression models [20]. Univariate and multivariate models were performed, adjusting for patient characteristics and ovarian stimulation variables (woman's age, gravity, parity, AFC, baseline FSH, total gonadotropin dose, stimulation protocol, use of IVF or intra cytoplasmic sperm injection (ICSI), and quality of embryo transferred).

Results

Table 1 shows the baseline characteristics of the patients. There were 543 single blastocyst transfers performed by six attending physicians and 389 single blastocyst transfers performed by 14 fellows (200 transfers by senior fellows and 189 by junior fellows). There were no differences in patient's age,

Table 1 Comparable baseline characteristics of patients who underwent blastocyst transfer performed by attending physicians or by fellows in training (data are presented as mean (SD) and *N* (%))

Variables		Attending staff <i>n</i> = 543	Fellows <i>n</i> = 389
Age (years)		34.48 (3.92)	34.66 (4.02)
BMI (kg/m ²)		24.90 (6.06)	25.70 (6.15)
Previous pregnancies		0.82 (1.19)	0.80 (1.20)
Previous term deliveries		0.32 (0.61)	0.28 (0.52)
Infertility duration (years)		3.40 (2.35)	3.61 (2.78)
Baseline FSH (IU/L)		7.47 (3.26)	7.16 (2.30)
Baseline estradiol (pmol/L)		213.69 (843.06)	181.76 (344.92)
AFC		18.16 (11.68)	18.07 (12.27)
TSH (IU/L)		1.74 (0.94)	1.69 (0.98)
First HCG (IU/L)		180.53 (238.51)	153.75 (230.25)
Infertility diagnosis	Male factor	192 (35.8%)	122 (31.6%)
	Anovulation	45 (8.4%)	31 (8.0%)
	Tubal factor	48 (9.0%)	39 (10.1%)
	Unexplained	118 (22.0%)	85 (22.0%)
	Single/same sex	15 (2.8%)	22 (5.7%)
	Endometriosis	27 (5.0%)	29 (7.5%)
	Combined	46 (8.6%)	25 (6.5%)
	Diminished ovarian reserve	45 (8.4%)	33 (8.5%)
Sperm	Fresh	477 (88.0%)	334 (86.3%)
	Frozen	11 (2.0%)	9 (2.3%)
	Surgical sperm extraction	25 (4.6%)	15 (3.9%)
	Donor sperm	29 (5.4%)	29 (7.5%)
Smoking	Yes	43 (8.8%)	32 (9.5%)
	No	444 (91.2%)	306 (90.5%)
Stimulation protocol	Fixed antagonist	312 (57.7%)	259 (66.9%)
	Long agonist	130 (24.0%)	63 (16.3%)
	Microdose flare	97 (17.9%)	64 (16.5%)
	Other	2 (0.4%)	1 (0.3%)
Fertilization	IVF	119 (22.0%)	85 (21.9%)
	ICSI	400 (73.8%)	284 (73.0%)
	50% IVF/50% ICSI	19 (3.5%)	18 (4.6%)
	Rescue ICSI	4 (0.7%)	2 (0.5%)
Freezing	Yes	392 (72.2%)	282 (72.5%)
	No	151 (27.8%)	107 (27.5%)
Quality of embryo transferred	Good	461 (84.9%)	349 (89.7%)
	Average	31 (5.7%)	14 (3.6%)
	Poor	47 (8.7%)	21 (5.4%)
	Unknown	4 (0.7%)	5 (1.3%)

Table 2 Comparable ovarian stimulation and IVF parameters of patients who underwent blastocyst transfer performed by attending physicians or by fellows in training

Variables	Attending staff <i>n</i> = 543 Mean (SD)	Fellows <i>n</i> = 389 Mean (SD)
Gonadotropin days	9.20 (1.81)	9.13 (2.03)
Gonadotropin dose (IU)	2402.01 (1360.85)	2417.68 (1406.37)
Peak estradiol level (pmol/L)	6161.37 (3202.38)	5977.04 (3258.52)
Endometrial thickness (mm)	10.41 (2.39)	10.68 (5.99)
Number of MII oocytes	9.25 (4.60)	8.91 (4.63)
Total number of blastocysts	2.81 (1.78)	2.82 (1.97)
Number of frozen blastocysts	1.92 (1.94)	2.06 (2.15)

gravity, parity, duration of infertility, BMI, tests of ovarian reserve, infertility diagnosis, and smoking status between patients who had transfers performed by fellows or by attending staffs. Table 2 demonstrates ovarian stimulation and IVF parameters. The number of eggs collected, dose of gonadotropins used, total number of blastocysts achieved, type of sperm used (fresh vs. frozen), use of intracytoplasmic sperm injection, and quality of the embryo transferred were comparable (Tables 1 and 2).

Cycle outcomes are shown in Table 3. Transfer performed by attending physicians or fellows resulted in similar clinical pregnancy rates (46.5 vs. 42.9%, $p = 0.28$) and live birth rates (38.3 vs. 34.2%, $p = 0.11$). There were no differences in the level of first serum β HCG, pregnancy outcome, delivery mode, birthweight, or gestational age at birth. When transfers performed by attending physicians were compared to those performed by junior fellows, the clinical pregnancy rates (46.5 vs. 43.8%, $p = 0.53$) and live birth rates (38.3 vs.

35.1%, $p = 0.41$) were also similar. The same trend was seen in transfers performed by staffs compared to those performed by senior fellows (clinical pregnancy rate 46.5 vs. 42.4%, $p = 0.34$ and live birth rate 38.3 vs. 33.3%, $p = 0.22$). Multivariate logistic regression analysis showed that even after adjusting for possible confounders (age, gravity, parity, baseline FSH, antral follicle count, dose of gonadotropins, stimulation protocol, and quality of embryo transferred), the clinical pregnancy rates (OR 0.81, CI 0.62–1.07) and live birth rates (OR 0.79, CI 0.6–1.05) among the two groups remain comparable.

Amongst the two groups of fellows, there were no differences seen in CPR or LBR after adjusting for the possible confounders mentioned above. Similarly, comparison of the outcomes after the first 10 single blastocyst transfers versus the later transfers per fellow showed no significant differences, although absolute numbers are small. Pooling the data from all fellows, the clinical pregnancy rate in transfers 1–25 was 39%.

Table 3 Comparable cycle outcome of patients who underwent blastocyst transfer performed by attending physicians or by fellows in training

Variables	Attending staff <i>n</i> = 543 Mean (SD)	Fellows <i>n</i> = 389 Mean (SD)
First HCG (IU/L)	180.53 (238.51)	153.75 (230.25)
Gestational age at birth (weeks)	38.34 (2.42)	38.17 (2.45)
Birth weight (grams)	3314.61 (578.62)	3267.60 (623.39)
Clinical pregnancy	253 (46.6%)	168 (43.2%)
Live birth	208 (38.3%)	133 (34.2%)
Pregnancy outcome		
Live birth	208 (82.2%)	133 (78.7%)
Miscarriage	38 (15.0%)	28 (16.6%)
Ectopic pregnancy	2 (0.8%)	3 (1.8%)
Unknown	0 (0.0%)	4 (2.4%)
Intrauterine fetal demise	3 (1.2%)	0 (0.0%)
Termination	2 (0.8%)	1 (0.6%)
Delivery mode		
Vaginal delivery	123 (59.7%)	84 (66.7%)
Planned cesarian section	39 (18.9%)	21 (16.7%)
Emergency cesarian section	41 (19.9%)	16 (12.7%)
Instrumental delivery	3 (1.5%)	5 (4.0%)
Gender of infant		
Female	95 (45.7%)	52 (39.7%)
Male	113 (54.3%)	79 (60.3%)

Discussion

The results of our study show that the pregnancy rates after ET performed either by fellows and or by attending physicians are similar. It suggests that the skill of performing an embryo transfer can be learned easily with pregnancy rates approaching those performed by experienced reproductive endocrinologists after a short period of training [21]. Barber et al. reported that the pregnancy rates after ET performed by nursing staffs and physicians were similar [22]. They also showed that embryo transfer performed by nurses in training was associated with reliable pregnancy rates [23]. Sinclair et al. reported similar results [24]. It suggests that with appropriate training and monitoring, ETs performed by trainees have similar success rates to those performed by experienced staff.

Papageorgiou et al. evaluated the number of ETs required to reach the efficiency of trained reproductive endocrinologists. The number varied among individuals; however, by 40–50 embryo transfers, the pregnancy rates were indistinguishable to those performed by trained reproductive endocrinologists [21]. The pregnancy rates for all fellows from 1 to 25 transfers were still reassuring at 39%. It further emphasizes that even though there may be a slight initial learning curve, the skill can be acquired rapidly by fellows in training. Our data was collected over a time period where IVF cycles were funded by the government of Quebec, and patients were entitled to three fresh IVF cycles per pregnancy. This meant that there was a high patient load during that time period, and fellows had many opportunities to perform ETs.

The limitations of our study included the fact that when a previous transfer was coded as difficult, or if the patient had failed multiple transfers, the embryo transfer was more likely to be done by the attending physician. Also, if a transfer happened on a weekend, they were done by attending physicians as the fellows were unavailable. If the fellow performing the transfer faced difficulty with the ET, then the attending staff was called to take over. We did not adjust in our data analysis for the difficulty of the ET, which could have potentially reduced pregnancy rates performed by attending physicians if they were only performing the difficult transfers. However, attending physicians were also performing all the transfers in two out of the 7 days per week suggesting that many of the transfers they performed were certainly routine, presumably easy, transfers.

The strength of our study includes a high proportion of embryo transfer performed by fellows in training (394 embryo transfer). To the best of our knowledge, our data represent the largest series of embryo transfer performed by fellows; they performed 42% of embryo transfers in the clinic. A similar finding was reported by Eaton et al. [11]. In their study, fellows performed only 104 embryo transfers over a period of over 5 years. During this time, changes might have occurred in

the treatment protocols and embryology laboratory techniques. In addition, we evaluated live birth rates in addition to clinical pregnancy rates. We also included only single fresh blastocyst transfers, limiting heterogeneity in embryo development, and the ability to control for some aspects of embryo quality.

Patient baseline characteristics and ovarian stimulation parameters were similar between cycles performed by attending staff and fellows. It suggests that attending staff were not more likely to perform transfer on poor prognosis patients. Further, after adjusting for the quality of embryo, our multivariate analysis showed no differences in clinical pregnancy and live birth rates between transfers performed by fellows and attending physicians.

We are aware of the challenges present in private training programs particularly where a patient may request an attending physician to do their transfer. However, from our experience, patients are reassured when the transfer is performed under ultrasound guidance and they too can see the catheter placement and the embryo flash. Often the attending staff is present even when not performing the embryo transfer. Our patients are also aware that there are comparable pregnancy rates between transfers performed by fellows and those performed by attending staff and that pregnancy rates per physician (whether staff or fellow) are continuously monitored. In an environment when all nursing and ancillary staff are also aware that the outcomes are comparable, this reinforces and reassures couples undergoing treatment that they are receiving good quality care whether an attending staff or a fellow performs their embryo transfer.

We conclude that clinical pregnancy rate and live birth rate after embryo transfer performed by attending staff or fellows are comparable. This finding reassures fellowship programs that allowing fellows to perform embryo transfers does not compromise the outcome.

Compliance with ethical standards

The Research and Ethics Board of the McGill University Health Centre approved the study (Study 15-249).

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